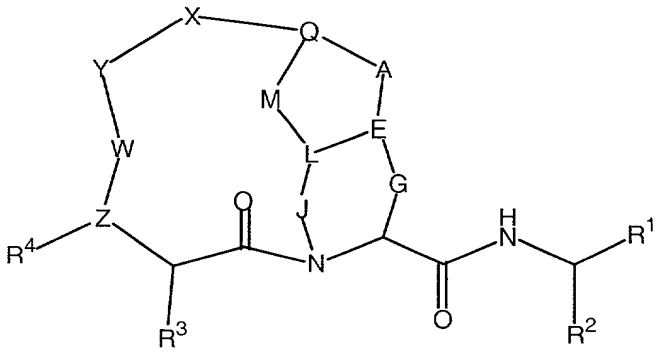
Claims

What is claimed is:

1. A macrocyclic compound, including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula I:



Formula I

wherein:

X and Y are independently selected from the moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl sulfide, alkyl-aryl sulfide, aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea, aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl -hydrazide, alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof, with the proviso that X and Y may optionally be additionally substituted with moieties selected from the group consisting of

aromatic, alkyl, alkyl-aryl, heteroalkyl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, alkyl sulfide, alkyl-aryl sulfide, alkyl sulfone, alkyl-aryl sulfone, alkyl amide, alkyl-aryl amide, alkyl sulfonamide, , alkyl amines, alkyl-aryl amines, alkyl-aryl sulfonamide, alkyl urea, alkyl-aryl urea, alkyl carbamate and alkyl-aryl carbamate;

$R^1 = COR^5$ or $B(OR)_2$, wherein R^5 = H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, COR^7 wherein R^7 = H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, or CH;

W may be present or absent, and if W is present, W is selected from C=O, C=S, or SO_2;

Q maybe present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M is also absent, and A is directly linked to X;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 or a bond;

E is CH, N or CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$,; and when G is absent, J is present and E is

directly connected to the carbon atom where G was connected to;

J maybe absent or present, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, SO_2, NH, NR or O; and when J is absent, G is present and E is directly linked to N;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be absent or present, and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; oxygen, nitrogen, sulfur, or phosphorus atoms with said oxygen, nitrogen, sulfur, or phosphorus atoms numbering zero to six;

(cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

2. The compound of claim 1, wherein $R^1 = COR^5$, and R^5 is H, OH, $COOR^8$, $CONR^9R^{10}$.

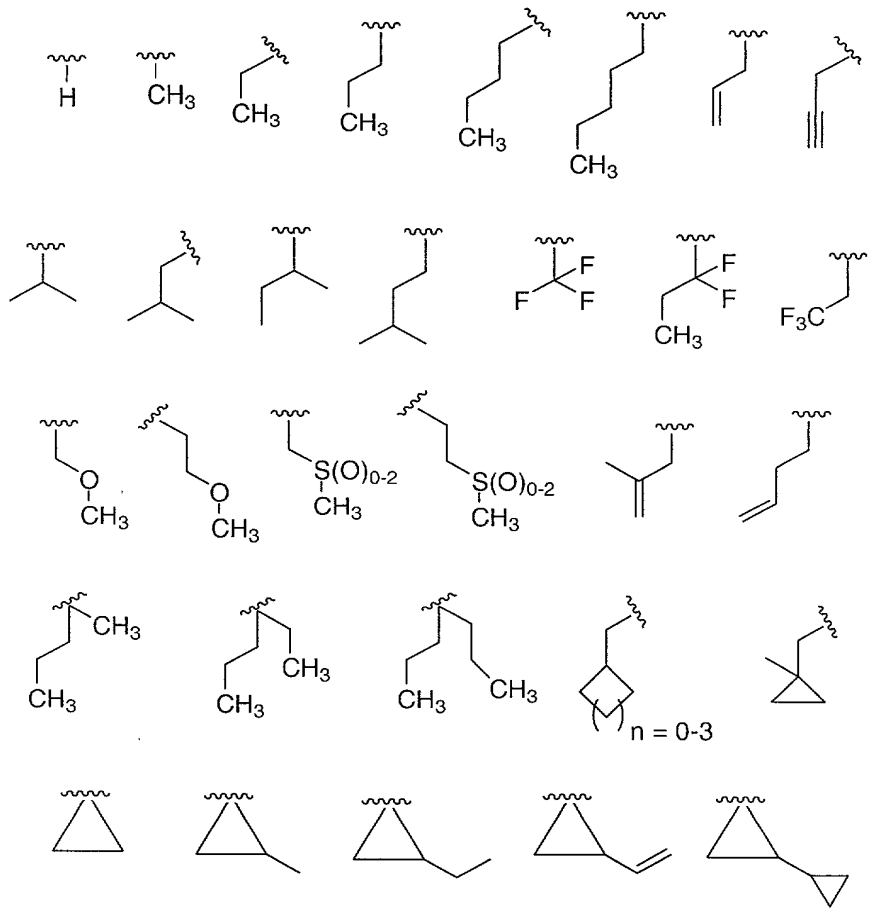
3. The compound of claim 2, wherein $R^1 = COCONR^9R^{10}$, and is R^9 is H, R^{10} is H, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})(R')$.

4. The compound of claim 3, wherein $R^{10} = CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cyclohexyl, cyclopentyl, cyclopropyl, piperidyl, pyridyl and 2-indanyl.

5. The compound of claim 4, wherein $R^{1'}$ is H.

6. The compound of claim 5, wherein $R^{2'}$ = phenyl, thiophenyl, cyclohexyl, 2-indanyl, cyclopentyl, pyridyl, phenyl(4-$HNSO_2NH_2$), R^{11} is H or *tert*-butyl, R^{12} and R^{13} are methyl, and R' is hydroxymethyl or tert-butoxymethyl.

7. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:



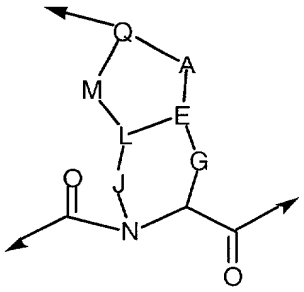
8. The compound of claim 7 wherein $R^1 = COR^5$, and R^5 is H, OH, $COOR^8$, $CONR^9R^{10}$.

9. The compound of claim 8 wherein L and M are absent, J is directly linked to E;

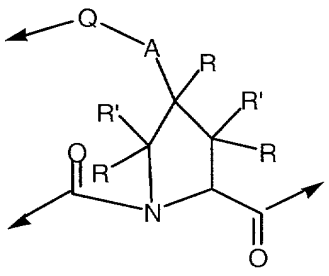
10. The compound of claim 8 wherein L, J and M are absent, E is directly linked to N;

11. The compound of claim 8 wherein G and M are absent.

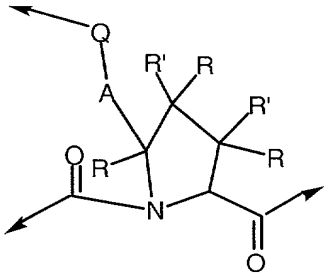
12. The compound of claim 8, wherein the moiety:



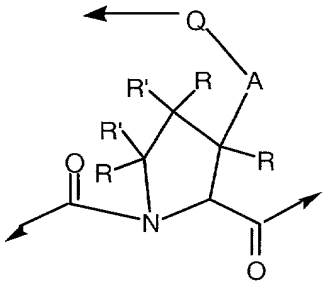
is selected from the group consisting of the following structures a, b, or c:



a

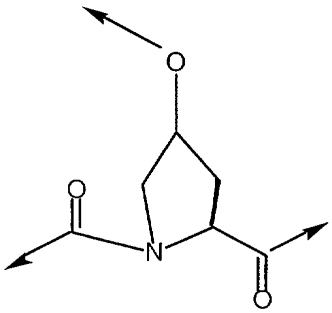


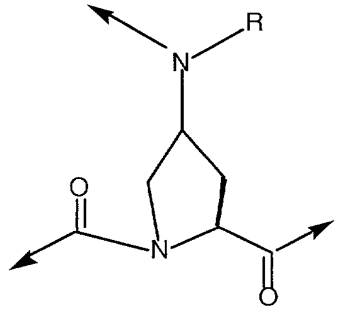
b

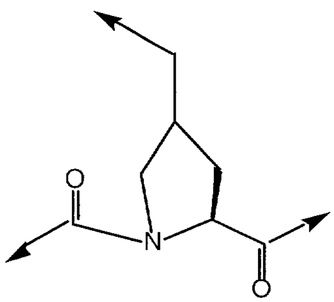


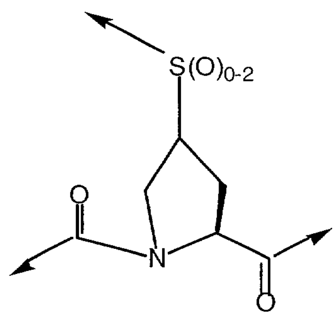
c

13. The compound of claim 12, wherein structure a is selected from the following structures:

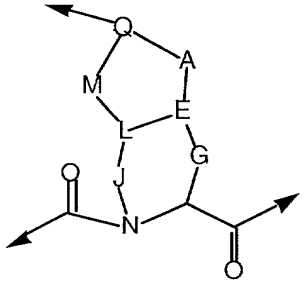




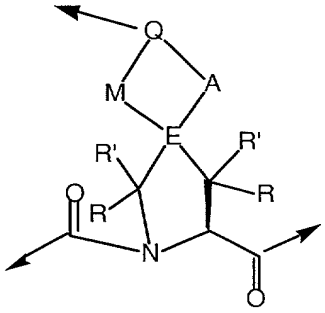




14. The compound of claim 8, wherein:



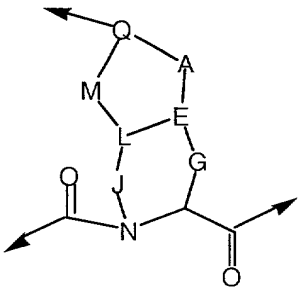
is



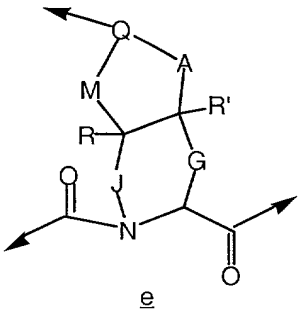
d

wherein M may be absent or present, and if M is absent, Q is linked to E.

15. The compound of claim 8, wherein:



is

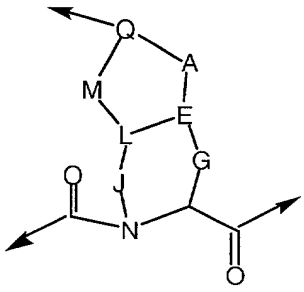


e

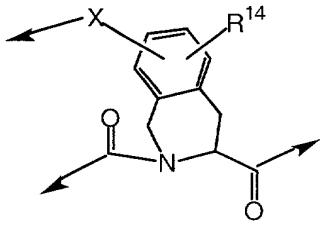
wherein G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and Q is CH, CR, or N.

16. The compound of claim 8, wherein G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and the moiety A-E-L-M-Q is an aromatic ring consisting of two to eight carbon atoms, zero to six hetero atoms with X and J being *ortho*, *para* or *meta* with respect to each other.

17. The compound of claim 16, wherein:



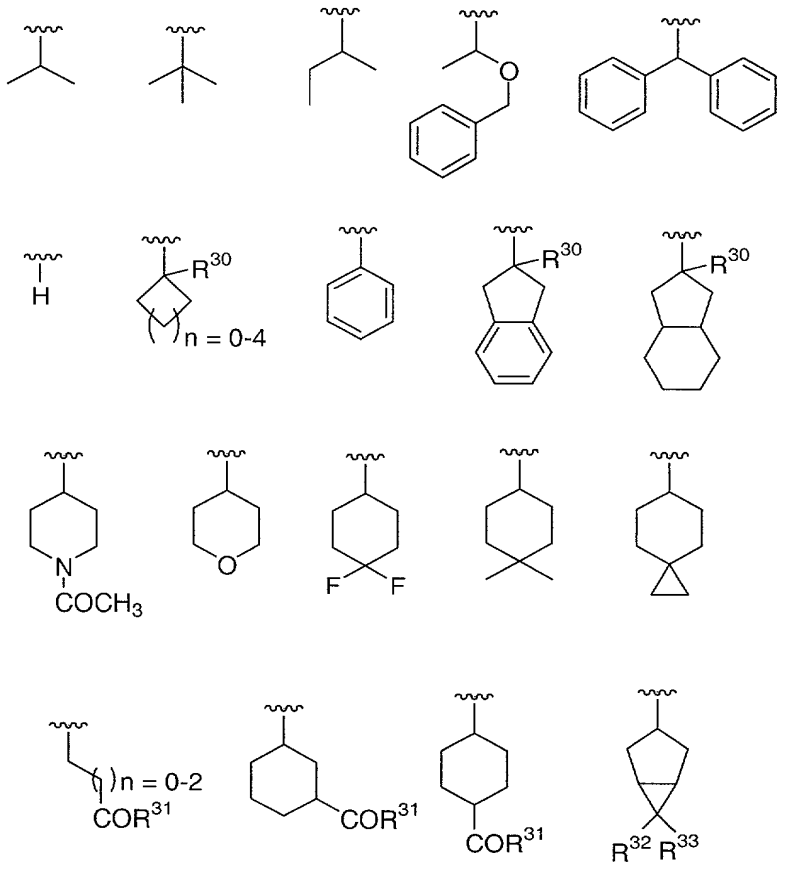
is



f

wherein R^{14} is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl.

18. The compound of claim 1, wherein R^3 is selected from the group consisting of:

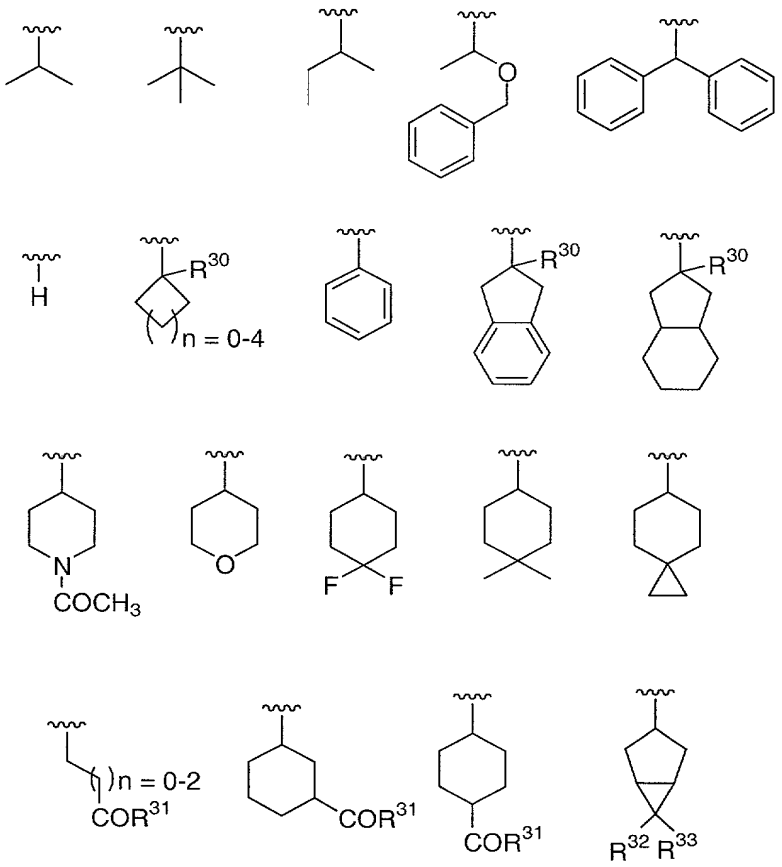


wherein R^{30} = H, CH_3 or other alkyl groups;

R^{31} = OH, O-alkyl, NH_2, N-alkyl; and

R^{32} and R^{33} may be the same or different and are selected independently from H, F, Cl, Br and CH_3.

19. The compound of claim 8, wherein R^3 is selected from the group consisting of:

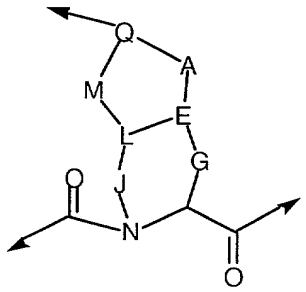


wherein wherein R^{30} = H, CH_3 or other alkyl groups;

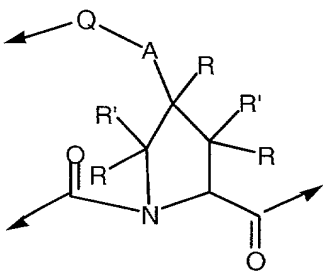
R^{31} = OH, O-alkyl, NH_2, N-alkyl; and

R^{32} and R^{33} may be the same or different and are selected independently from H, F, Cl, Br and CH_3 ,

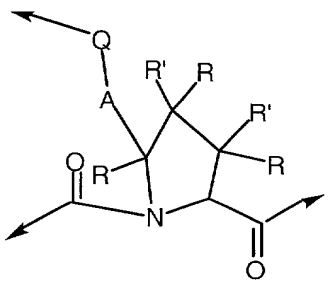
and the moiety:



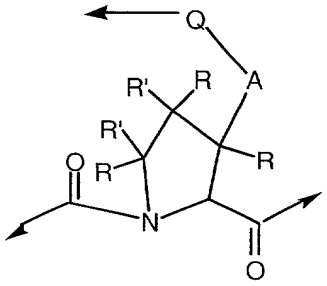
is selected from one of the following structures a, b, c, d, e, and f:



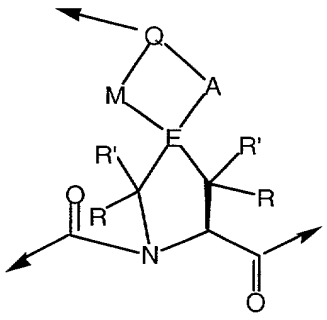
a



b

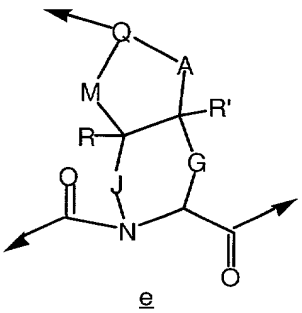


c



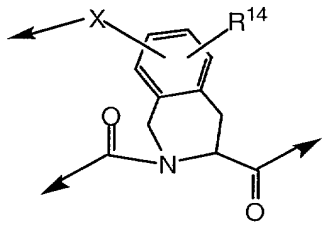
d

wherein M may be absent or present, and if M is absent, Q is linked to E;



e

wherein G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, or $(CRR')_p$, Q is CH, CR, or N; and



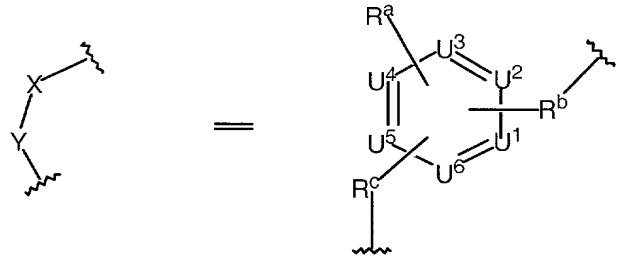
f

20. A compound of claim 19, wherein Z = N and R^4= H.

21. A compound of claim 20, wherein W is C=O.

22. A compound of claim 21, wherein the moiety X-Y is selected from the group consisting of: C1-C6 alkyl, O-alkyl, NR-alkyl.

23. A compound of claim 21, wherein:



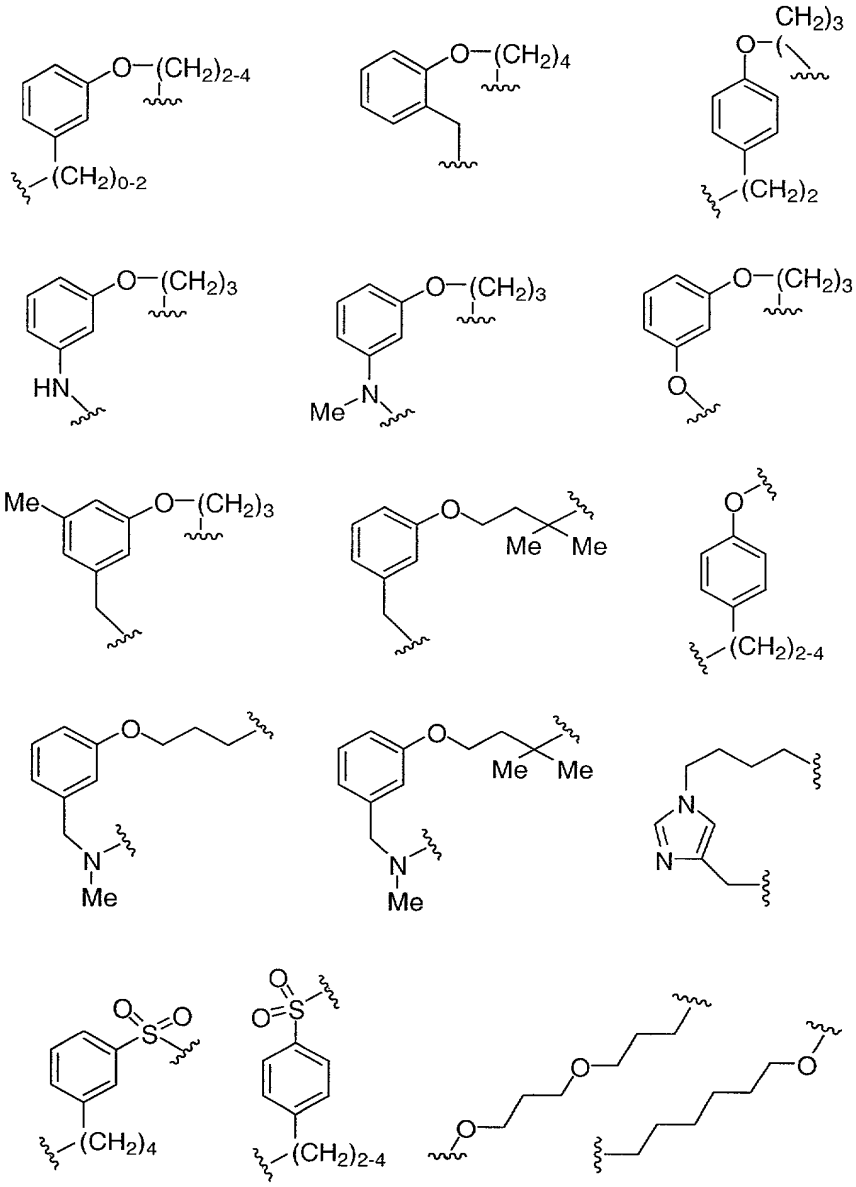
wherein R^b is connected directly to Q if Q is present or to A if Q is absent; R^c is connected to W; U^1 through U^6 can be part of a six membered carbon ring, or five or six membered ring with one or more heteroatoms;

R^a = H, alkyl, alkoxy, hydroxy, thio, halogen, nitro, cyano, carboxylic acid, ester, amide, amino, nitrile, or CF_3;

R^b is a bond, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, O, S, SO_2, NH, O(alkyl), S(alkyl), SO_2(alkyl) or N(alkyl); and

R^c is a bond, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, O, S, SO_2, NH, O(alkyl), S(alkyl), SO_2(alkyl), N(alkyl) or CH_2-N(alkyl) with the CH_2 being linked to the aromatic ring.

24. A compound of claim 21, wherein the moiety X-Y is selected from the group consisting of the following structures:



25. A pharmaceutical composition comprising as an active ingredient a compound of claim 1.

26. The pharmaceutical composition of claim 25 for use in treating disorders associated with HCV.

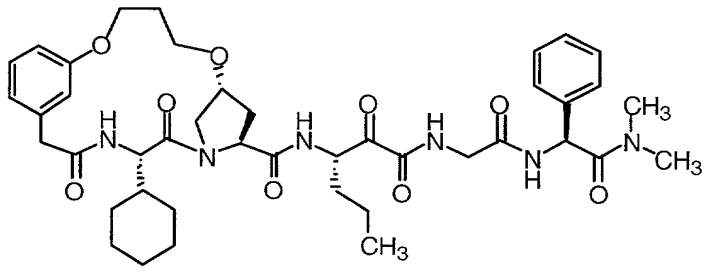
27. The pharmaceutical composition of claim 25 additionally comprising a pharmaceutically acceptable carrier.

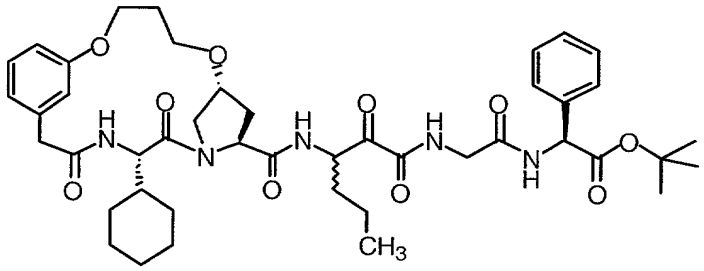
28. A method of treating disorders associated with the HCV protease, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of claim 1.

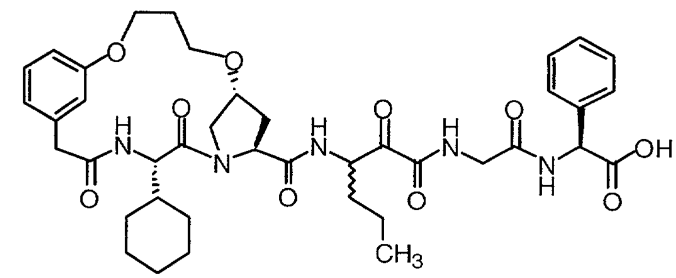
29. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV protease.

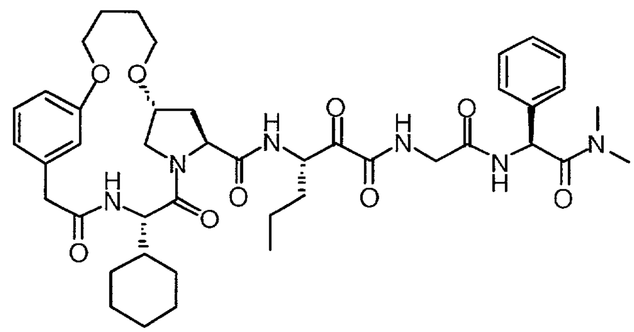
30. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV protease, said method comprising bringing into intimate contact a compound of claim 1 and a pharmaceutically acceptable carrier.

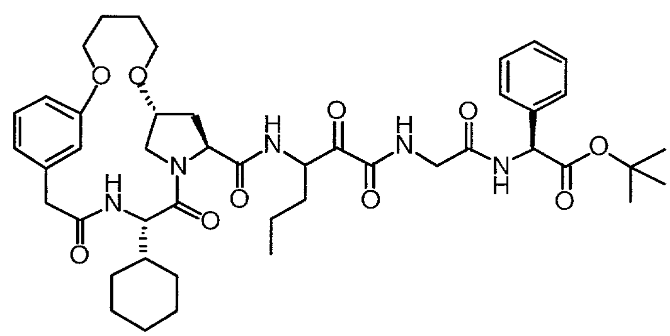
31. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

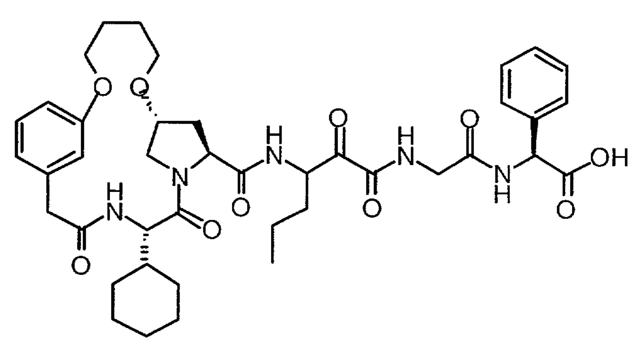


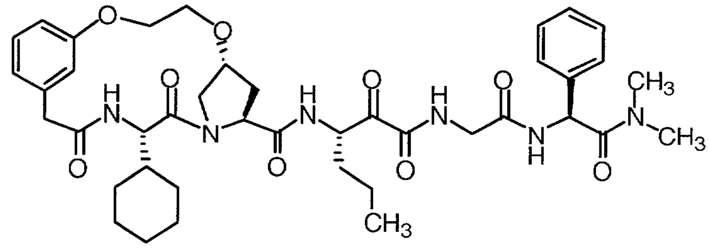


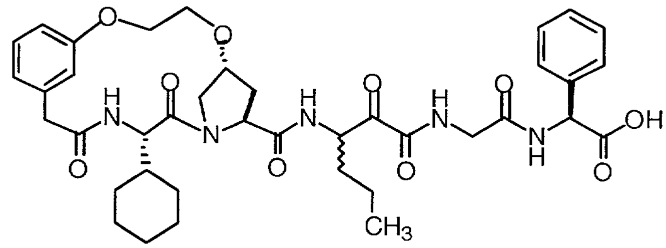


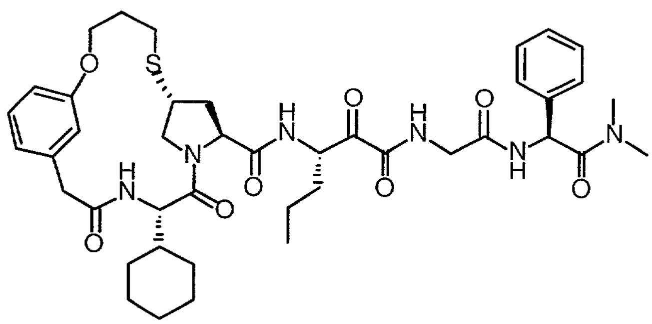


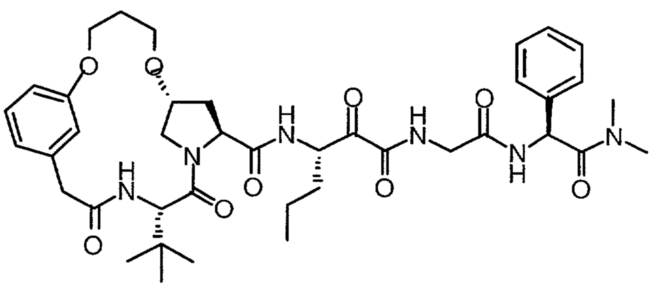


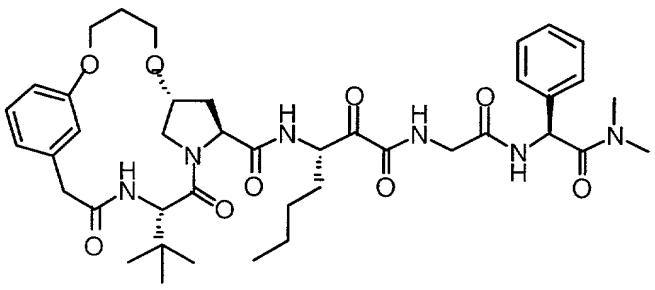


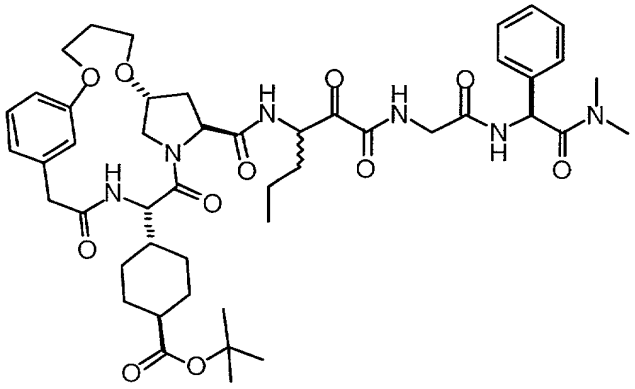


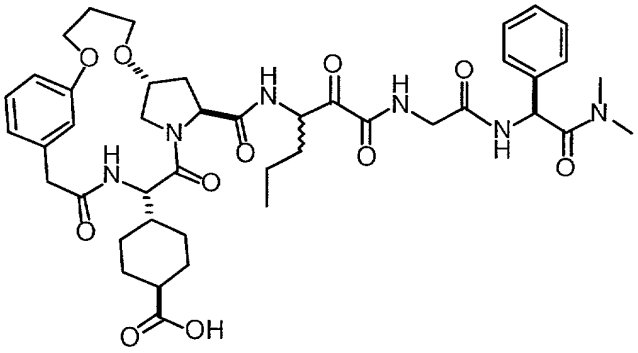


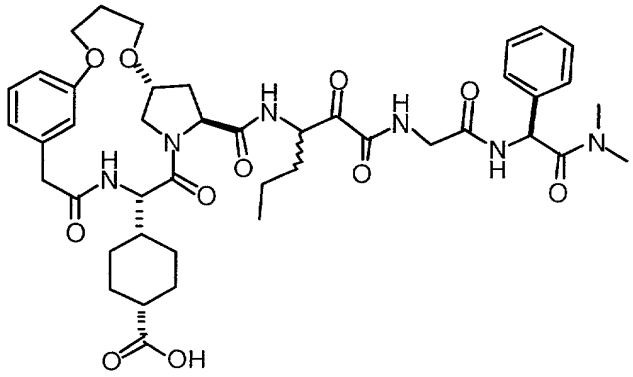


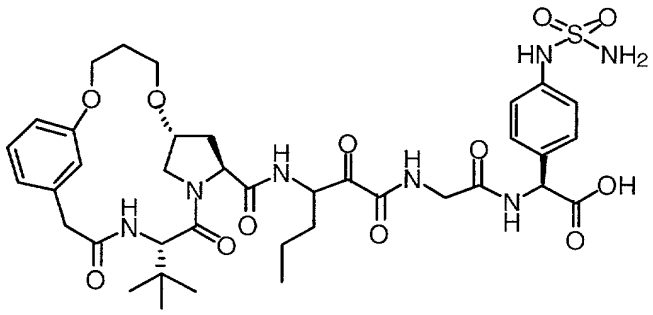


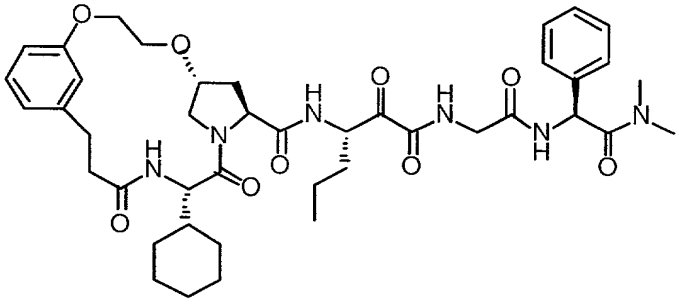


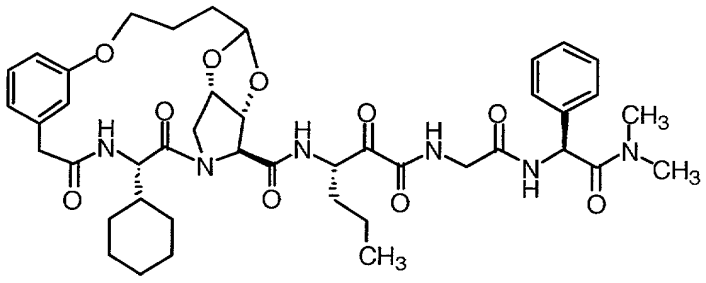


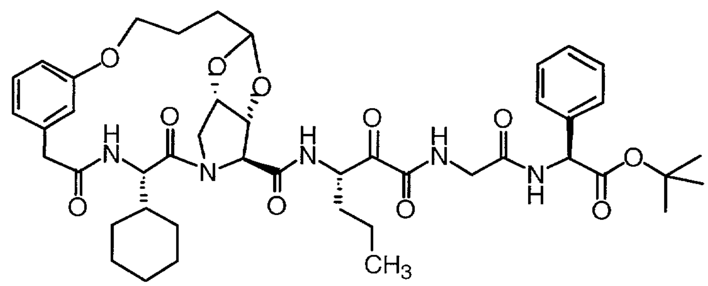


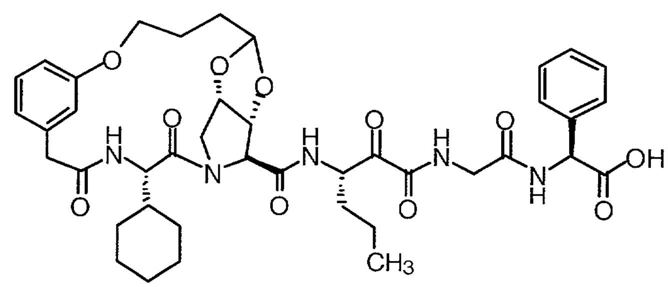


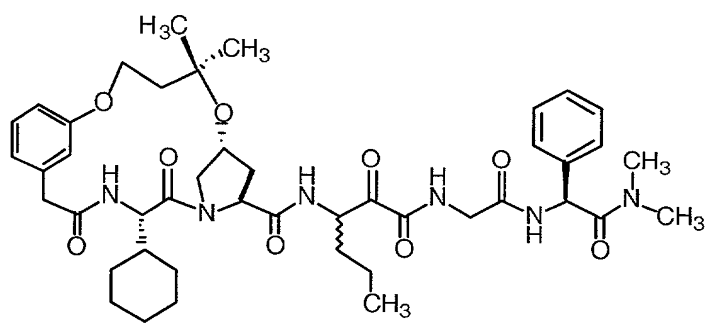


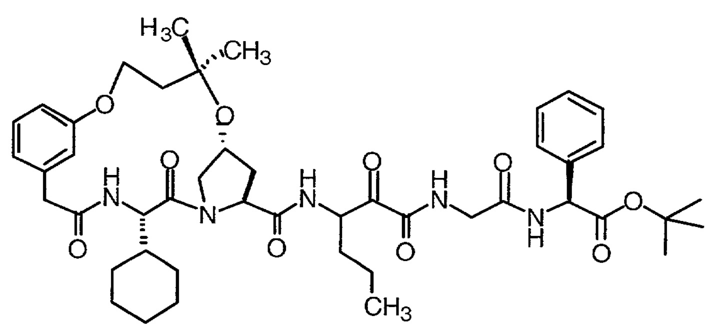


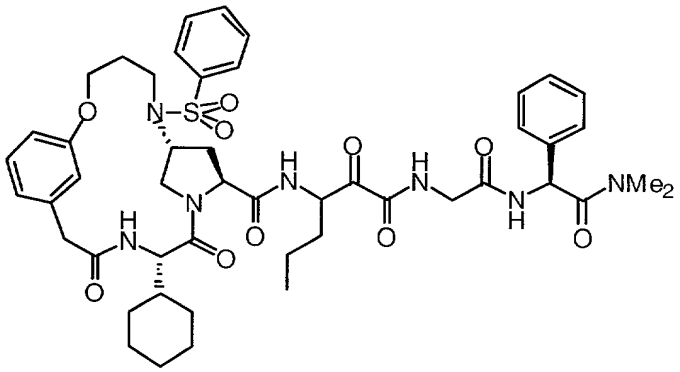


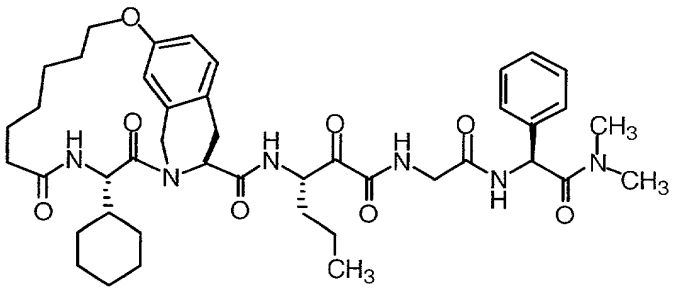


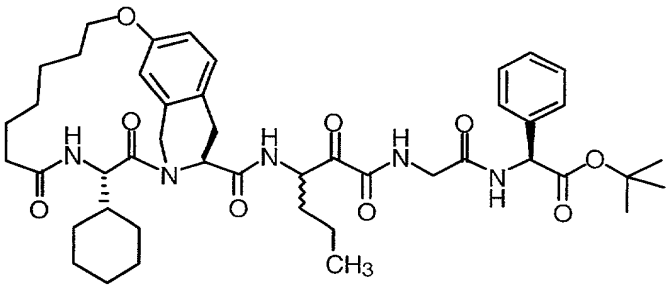


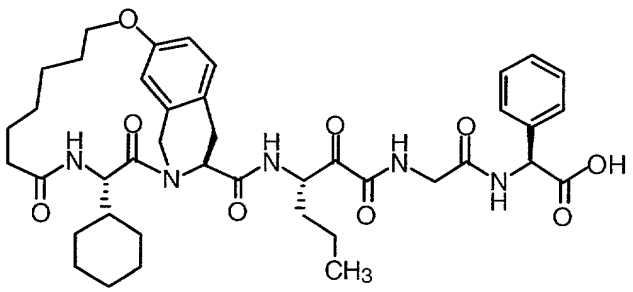


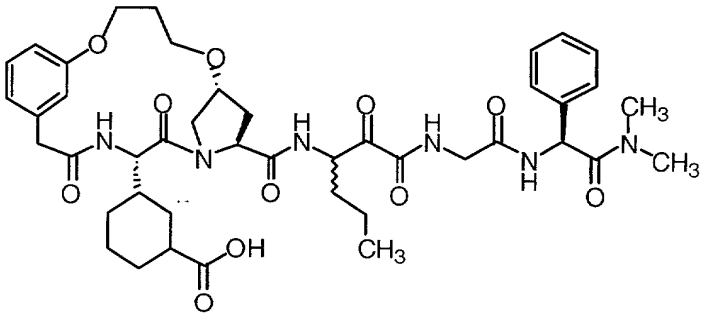


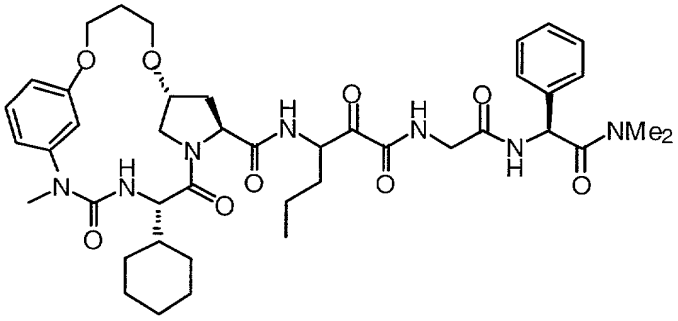


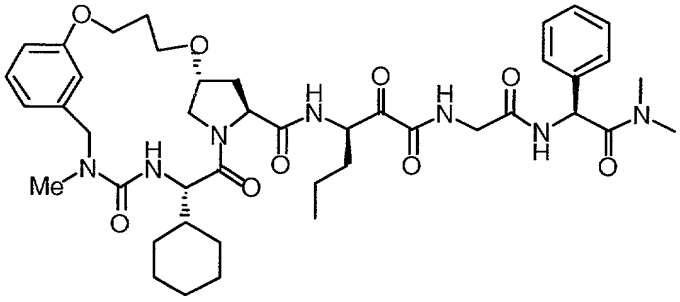


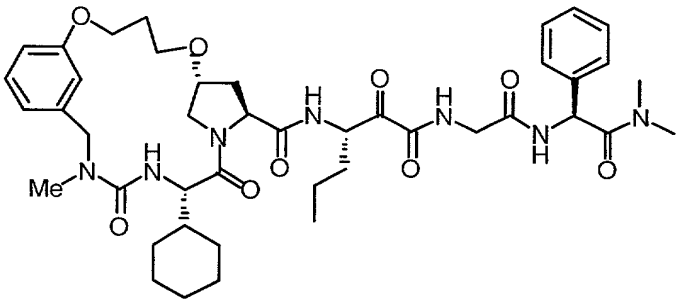


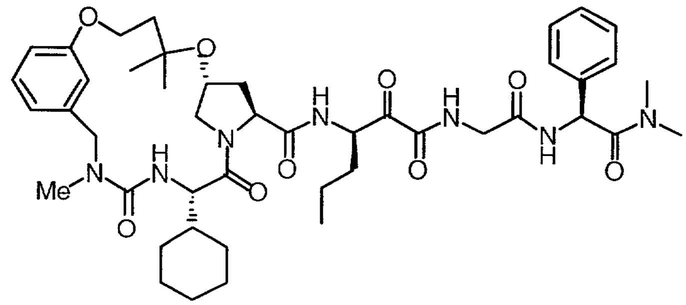


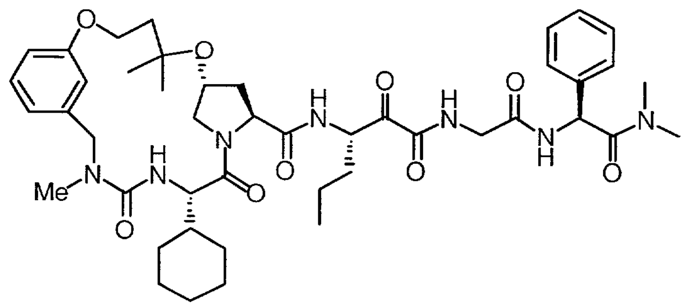


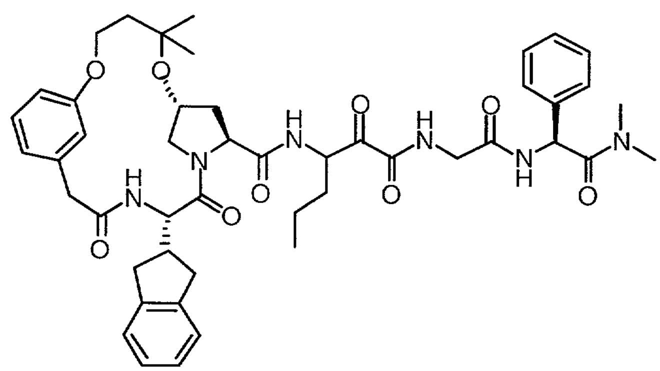


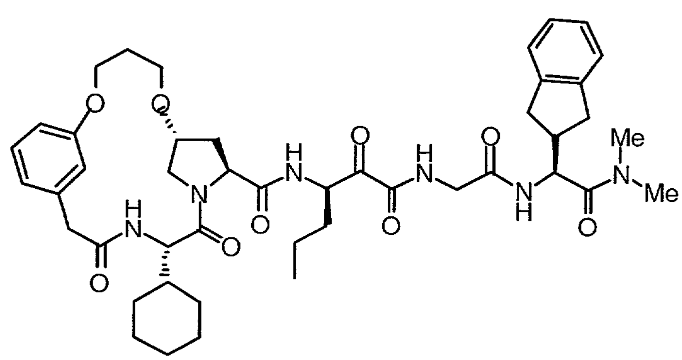


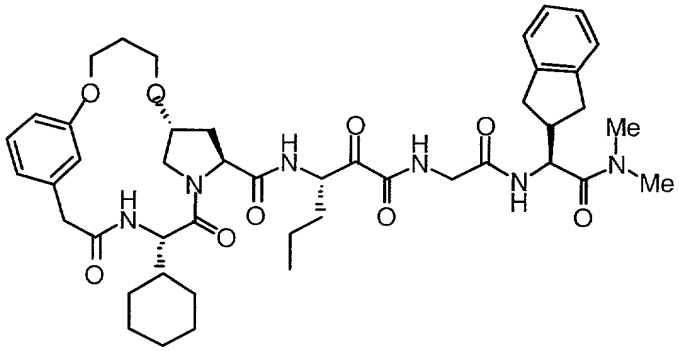


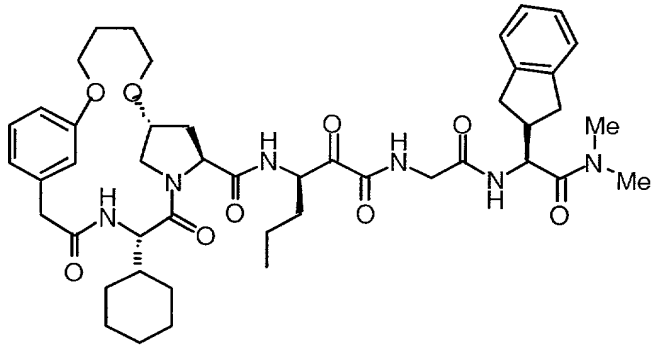


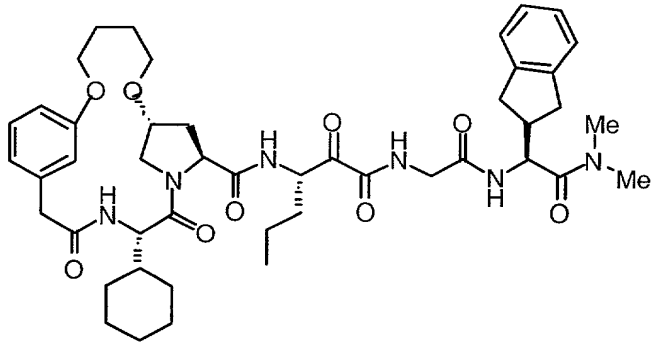


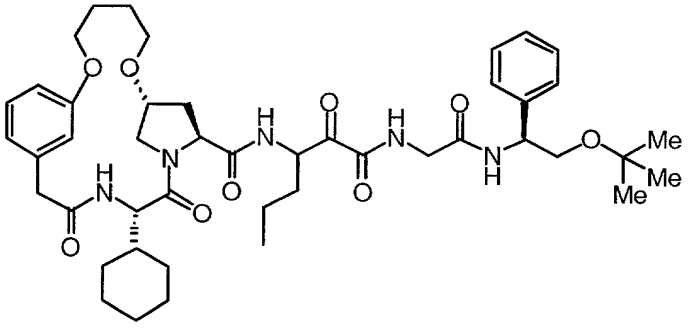


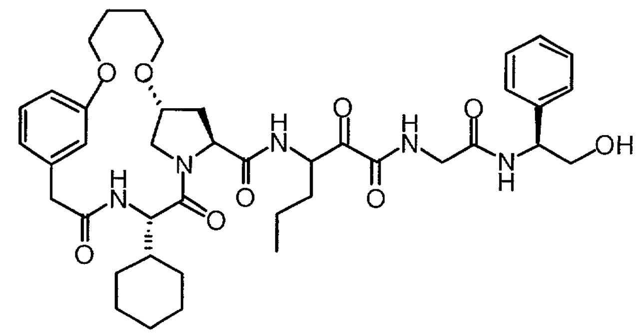


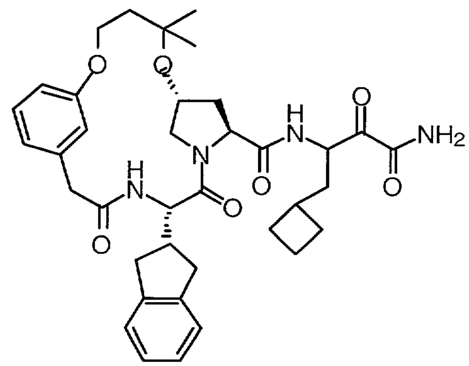


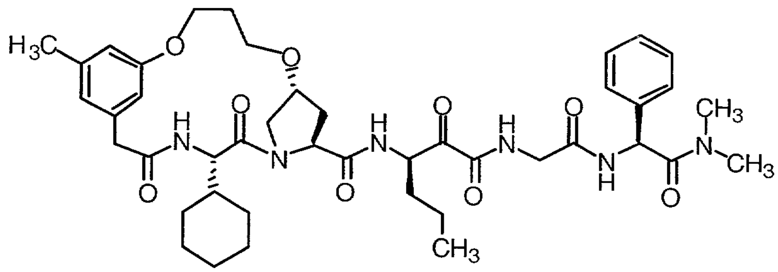


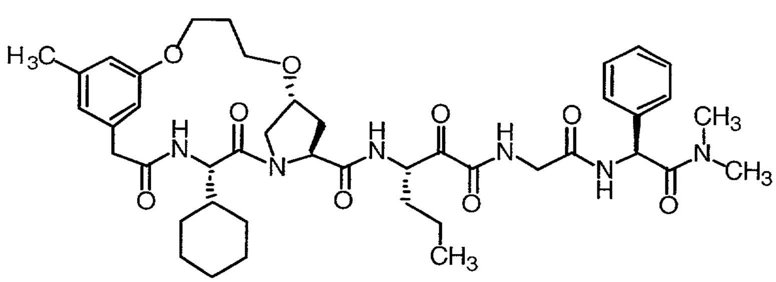


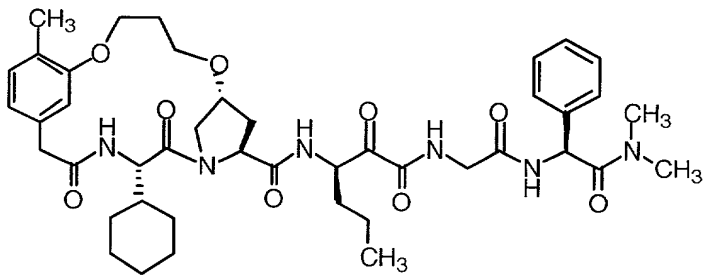


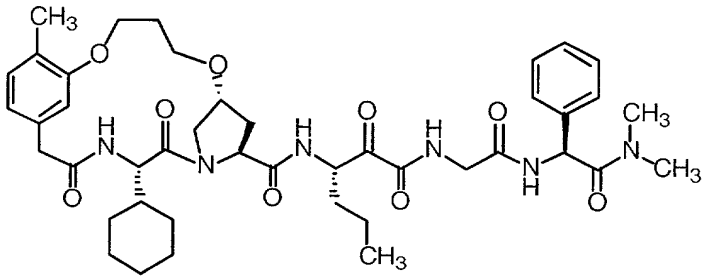


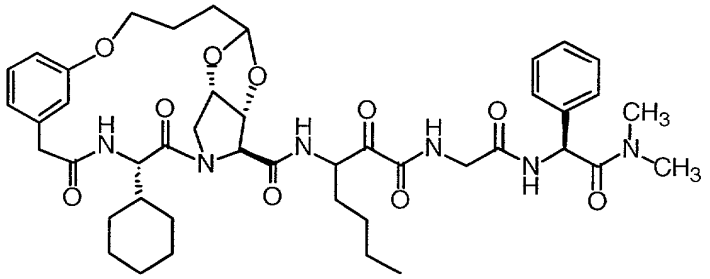


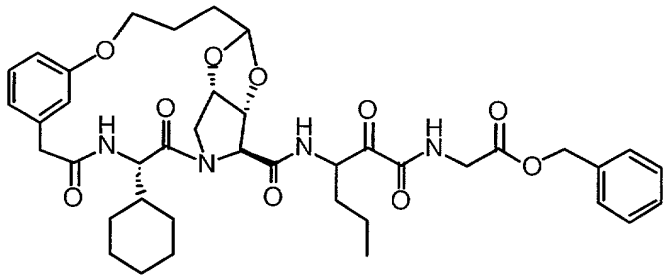


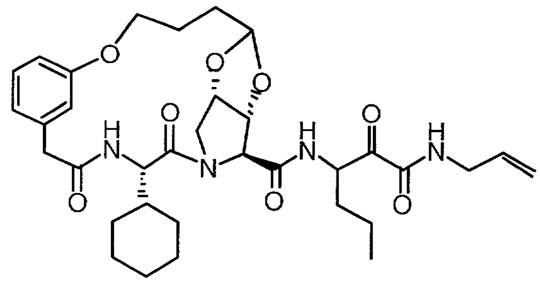








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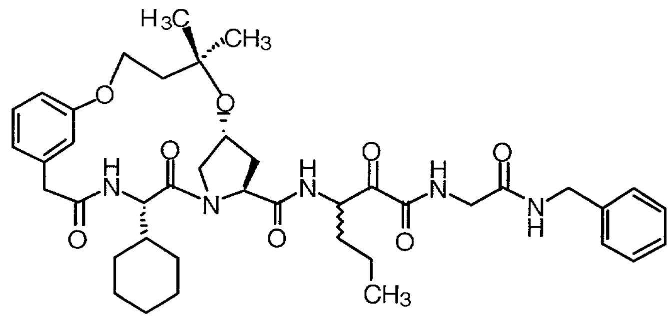
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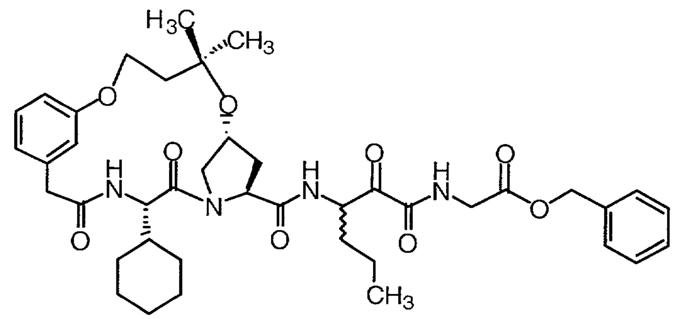
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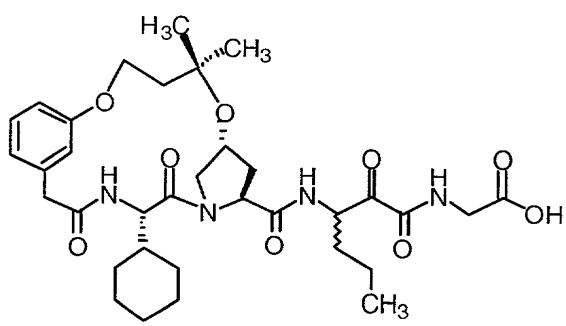
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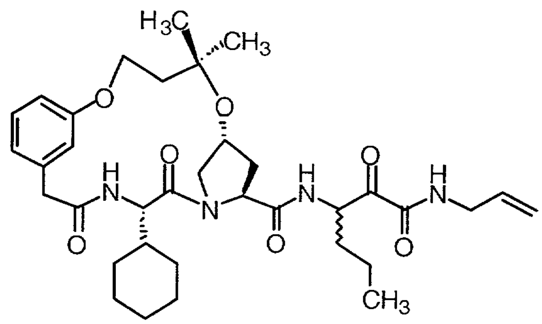
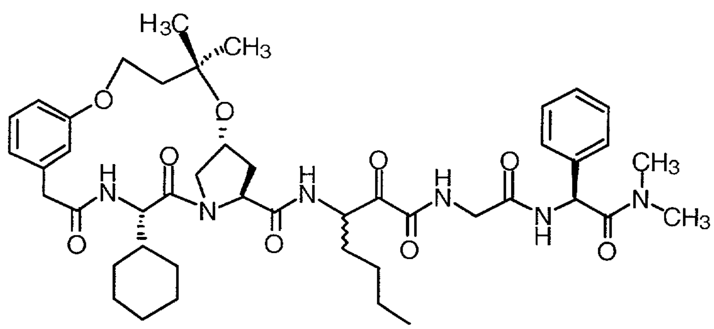
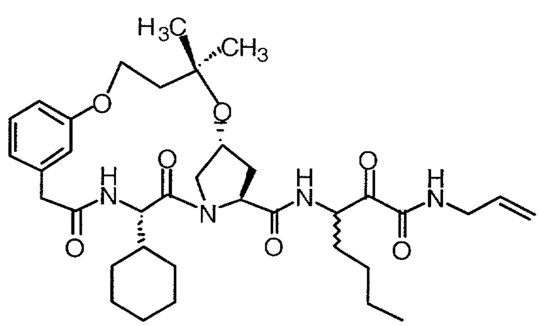
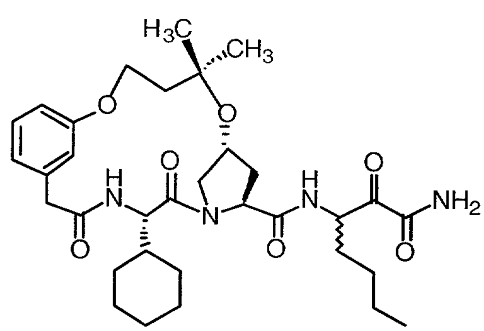
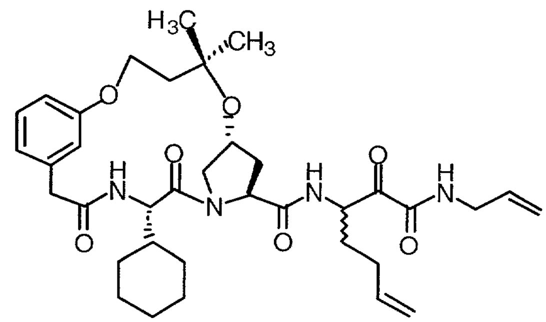
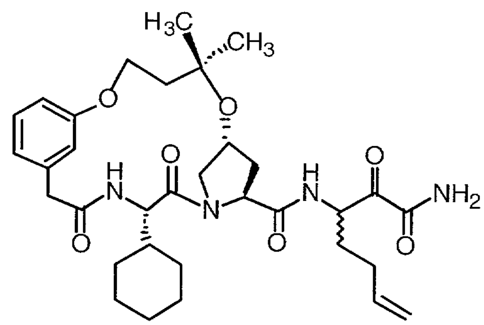


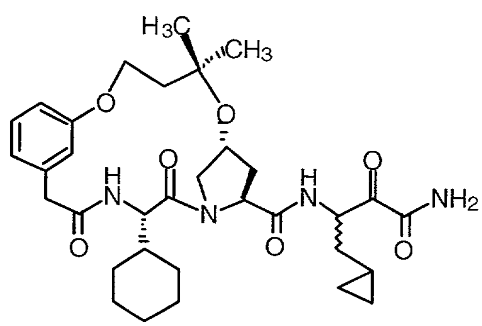


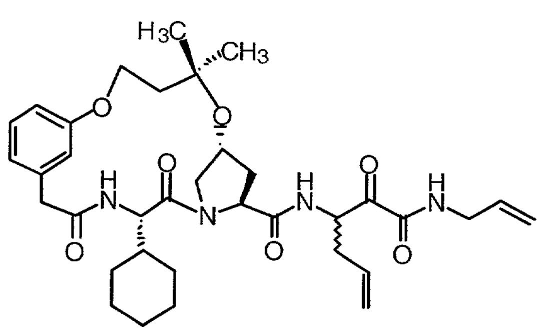


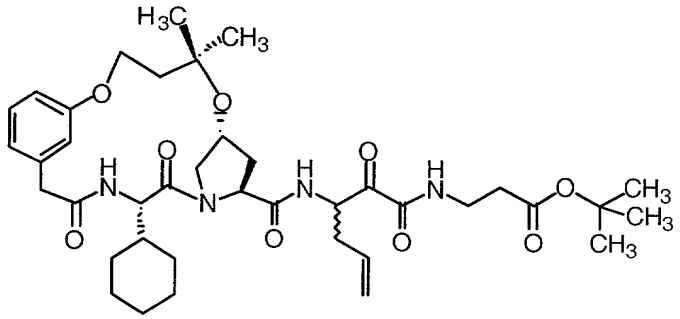


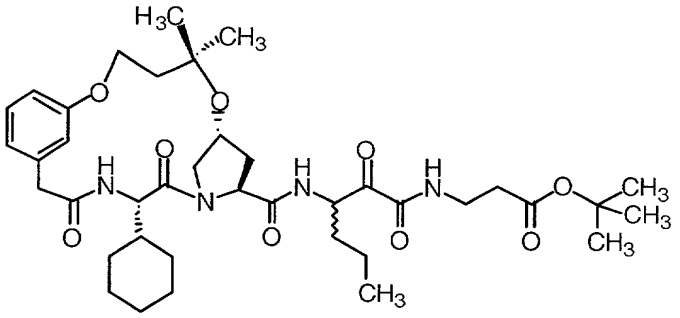


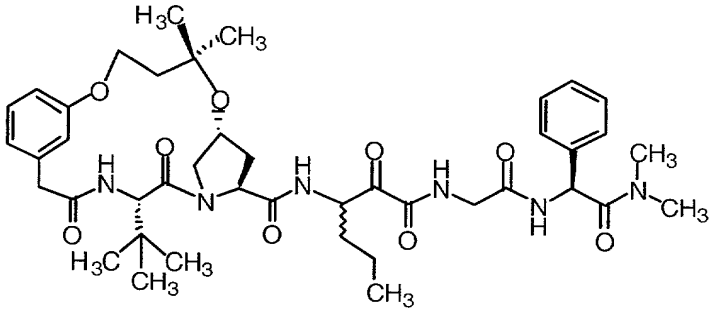


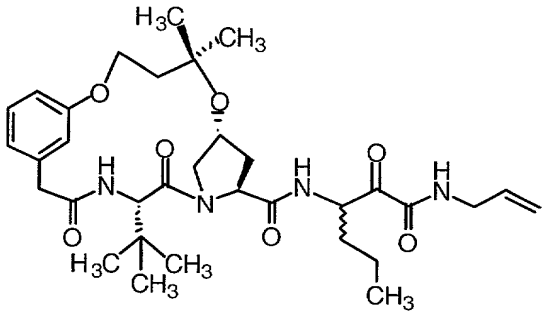


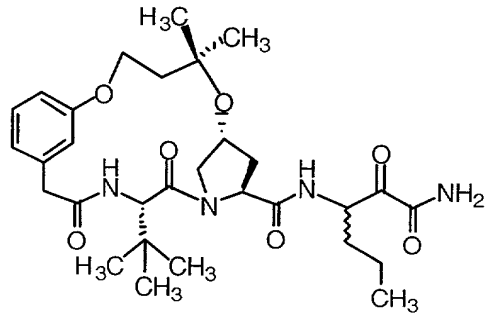


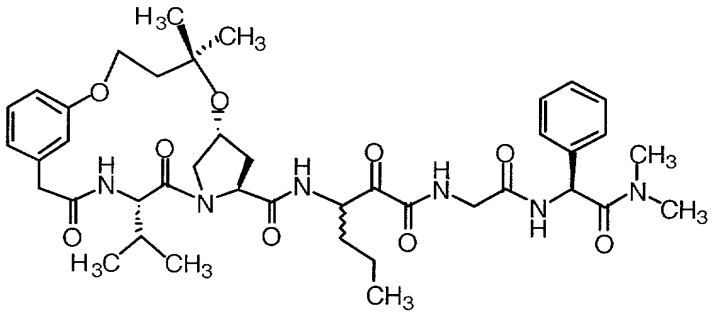


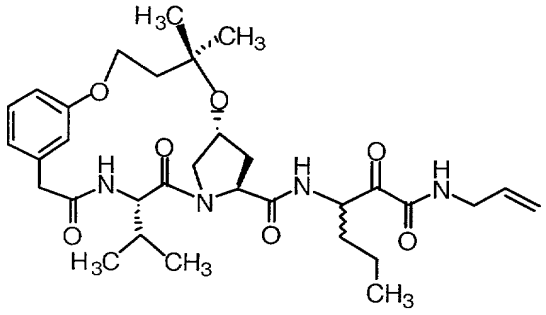


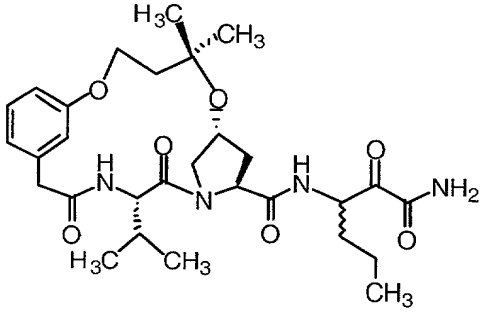


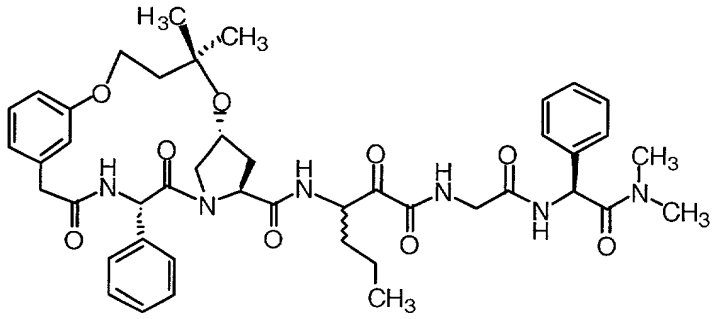


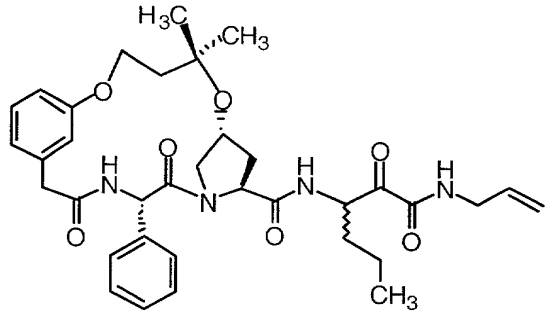


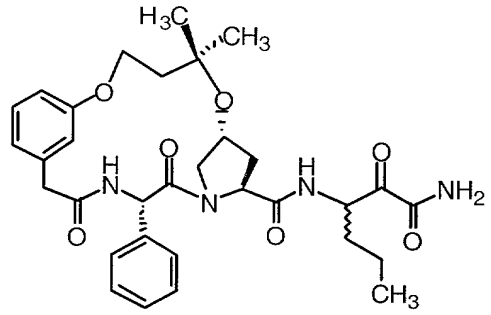


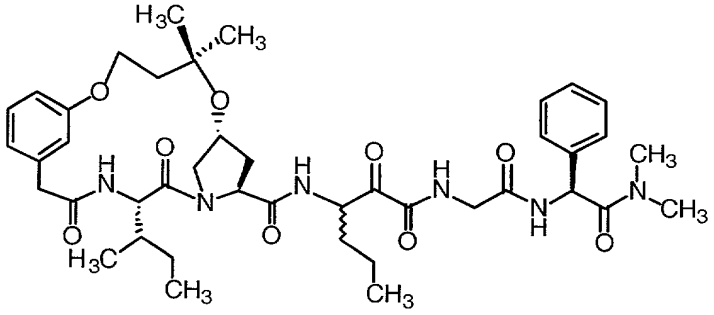


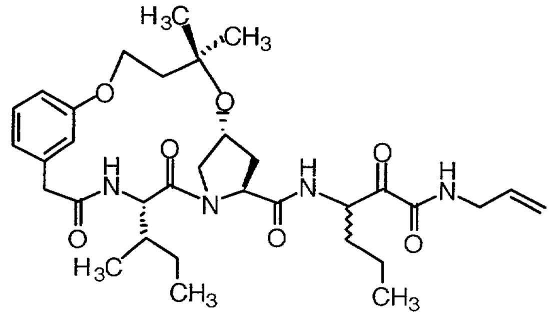


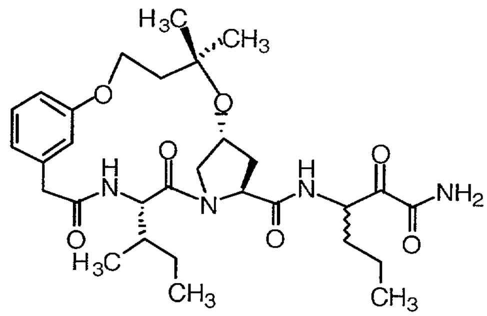


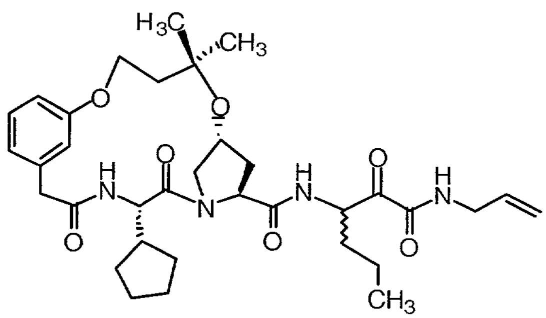


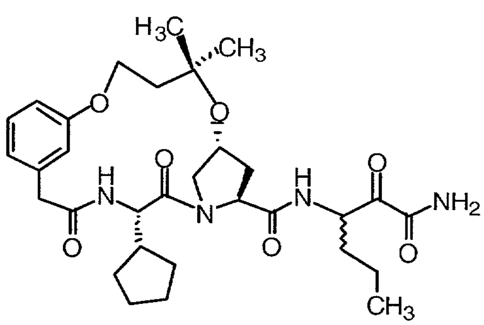


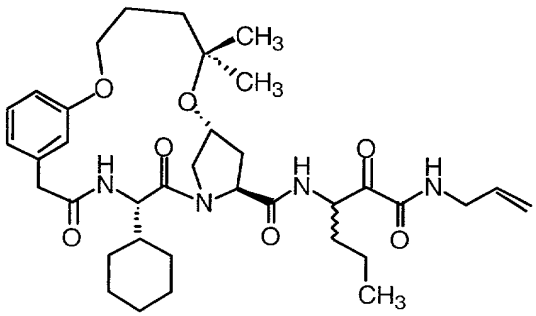


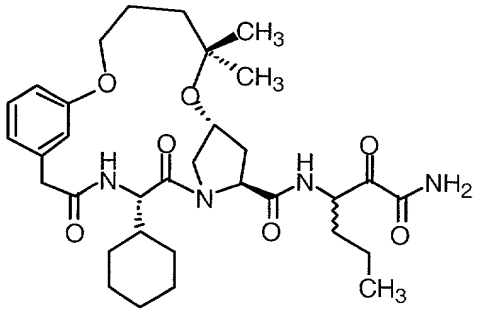


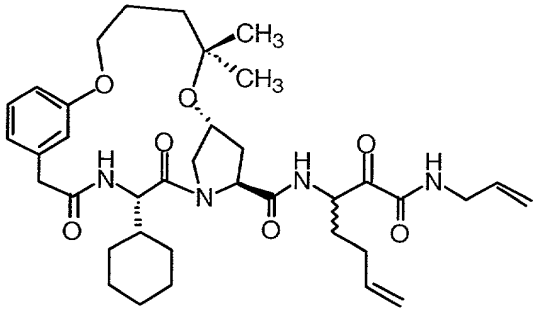


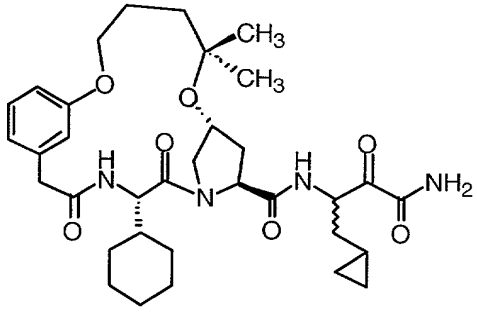


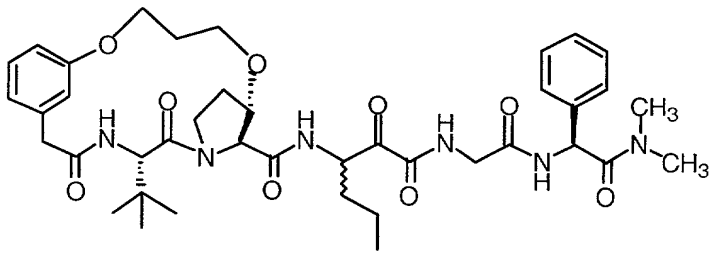


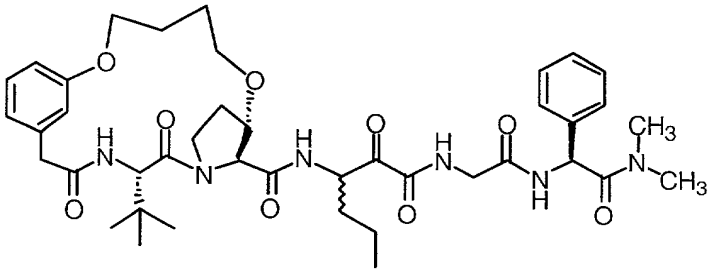












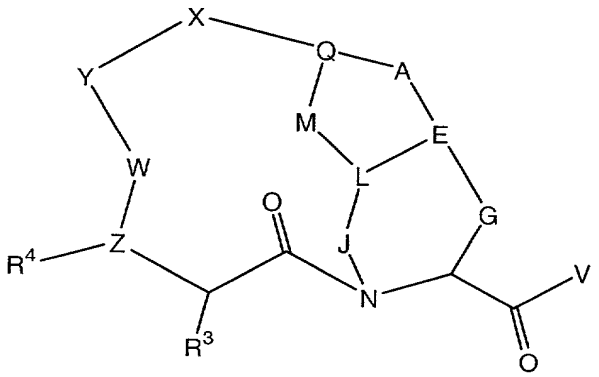
32. A pharmaceutical composition for treating disorders associated with the HCV protease, said composition comprising therapeutically effective amount of one or more compounds in claim 31 and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition of claim 32, additionally containing an antiviral agent.

34. The pharmaceutical composition of claim 32 or claim 33, still additionally containing an interferon.

35. The pharmaceutical composition of claim 34, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

36. A compound of the formula:



wherein V = OR or NHR, with R being H or alkyl; and X, Y, Q, A, M, W, L, E, G, J, Z, R^3 and R^4 are as defined in Claim 1.